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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,528	10/13/2000	David M. Stern	0575/62096/JPW/JML	8939

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,528	STERN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-5 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3,5 and 11-14* is/are allowed.

6)☒ Claim(s) *4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-25-05 has been entered.

Applicants' amendment filed 11-25-05 has been entered. Claim 3 has been amended. Claims 3-5 and 11-14 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reduction of smooth muscle proliferation and migration in carotid artery by treating Fatty Zucker rat with murine soluble RAGE (sRAGE) via intraperitoneal injection, does not reasonably provide enablement for a method for preventing exaggerated restenosis in a diabetic **human** subject by administering to said subject any sRAGE polypeptide in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claim is directed to a method for preventing exaggerated restenosis in a diabetic human by administering to said human a therapeutically effective amount of a human or mouse soluble receptor for advanced glycation endproducts (sRAGE) *in vivo*.

The specification discloses reduction of smooth muscle proliferation and migration in carotid artery by treating Fatty Zucker rat having carotid artery balloon injury with soluble RAGE (sRAGE) via intraperitoneal injection.

The claims encompass using human or mouse sRAGE to prevent exaggerated restenosis in a diabetic human subject *in vivo*. The specification fails to provide adequate guidance and evidence for how to prevent exaggerated restenosis in a diabetic human subject by administering to said subject a human or mouse sRAGE *in vivo*.

The claims read on preventing exaggerated restenosis in a diabetic human subject by administering to said subject a therapeutically effective amount of sRAGE. The biological environments in different organisms differ from each other physically and physiologically. Even if the sRAGE can function to prevent exaggerated restenosis in a rat model, the data from a rat model can not be extrapolated into success in preventing exaggerated restenosis in human.

The prior art teaches that successful application of restenosis treatments in small animal models is not predictive of success in other animals, particularly in humans. Muller et al., 1992 (J. Amer. Coll. Cardiol. 19(2):418-432) teach that, as of 1992, greater than 50 studies had shown that at least 9 different classes of pharmacological agents inhibit intimal proliferation in response to arterial injury in animal models. However, none of these agents reproducibly reduced the incidence of restenosis after coronary balloon angioplasty in humans. To explain these results, Muller considered the differences between the various systems. Significant interspecies and

intraspecies differences were found to exist among the various animal models, particularly with respect to the extent and composition of neointimal thickening, drug and lipid metabolism, and the activity of coagulation and fibrinolytic systems. Muller teaches that these differences may account for the variability in sensitivity of various animal models to treatments, and should be considered carefully in the interpretation of experimental studies (e.g. abstract). Muller further teaches that the amount of elastin in the media of coronary arteries of larger animals, such as dogs, pigs and baboons, are very similar to that of the human coronary artery but greater than that in small species, such as rodents and fowls, and thickness of the arterial intima varies among species (e.g. p. 420, left column). "Rat arteries differ morphologically from human arteries in that they have no vasa vasorum, have a very much thinner subintimal layer and have a relatively small elastin content in the media (e.g. p. 421, left column, lines 4-7).

Naka et al., 2004 (Arteriosclerosis, Thrombosis, and Vascular Biology, Vol. 24, p. 1342-1349) discuss various mouse and rat models for vascular complications of diabetes and points out the complex nature of murine/rodent models in dissection of the biological response to arterial injury superimposed on chronic hyperglycemia and states "[t]aken together, these considerations underscore the complexity of these model systems and suggest that preclinical testing of novel therapeutic targets in restenosis ultimately requires the use of species such as pigs, rabbits, or nonhuman primates before testing in human subjects" (e.g. p. 1347, right column, second full paragraph). It appears that testing of the therapeutic effect of RAGE on diabetic vascular disease in larger animal models, such as pigs, rabbits or nonhuman primates would be required before testing on the human subject. Park et al., 2001 (Circulation, Vol. 104, p. 815-819) state "This study has several limitations. The relevance of restenoic animal models

to human restenosis is unknown, and no single model has yet been shown to reliably predict restenosis in humans" (p. 819, left column under "Study Limitations"). Although fatty Zucker rat model has disease arteries and is a well-established model for type II diabetes, however, whether the data of fatty Zucker rat regarding the use of a drug or sRAGE to prevent exaggerated restenosis is predictive of the therapeutic effect of the drug or sRAGE in a diabetic human subject is still unknown. One cannot extrapolate success in preventing exaggerated restenosis in fatty Zucker rat into success in a diabetic human subject. Therefore, although animal studies are likely to provide important insights into the pathophysiology of vascular injury, Park states "no single model has yet been shown to reliably predict restenosis in humans".

In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use a human or mouse sRAGE to prevent exaggerated restenosis in a human. Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of skilled artisan which is high, and the breadth of the claims that it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Conclusion

Claim 4 is rejected. Claims 3, 5 and 11-14 are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER